IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| IN RE APPLICANT | : Jackowski *et al.* |
| INVENTION | : **Complement C3 Precursor Biopolymer Markers Indicative of Alzheimer's Disease** |
| SERIAL NUMBER | : 09/994,909 |
| FILING DATE | : November 23, 2001 |
| EXAMINER | : Chernyshev, Olga N. |
| GROUP ART UNIT | : 1649 |
| OUR FILE NO. | : 2132.090 |

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CERTIFICATE UNDER 37 CFR 1.8(a)
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**DECLARATION UNDER 37 CFR § 1.132**

I, Ferris H. Lander, do hereby declare as follows:

1. I am a registered Patent Agent and am authorized to represent the inventor's and assignee in the application entitled **"Complement C3 Precursor Biopolymer Markers Indicative of Alzheimer's Disease"**, having U.S. Application Serial No. 09/994,909, filed November 23, 2001.

2. In the Final Office Action mailed on August 30, 2005, claim 1 (as presented on May 4, 2005) was rejected under 35 USC 101 because the claimed invention allegedly is drawn to an invention

with no apparent or disclosed specific and substantial credible utility. Claim 1 was also rejected under 35 U.S.C. 112, first paragraph because since the claimed invention is not supported by either a clear asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

Specifically, the Examiner asserts that the instant specification fails to provide any evidence of record or rely on any prior art disclosure to support the assertion that the instant claimed fragment (amino acid residues 2-14 of SEQ ID NO:1) is useful for diagnosis or treatment of Alzheimer's disease.

3. Applicants submit that Figures 1 and 2, as originally filed, are "evidence of record" which supports Applicants' assertion of the usefulness of the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) for diagnosis and/or treatment of Alzheimer's disease. Figure 2 shows a mass spectral profile obtained from Band 1 of the gel shown in Figure 1. Figure 2 also lists the ions identified from Band 1, including the claimed SEQ ID NO:1; an ion of complement C3 precursor protein weighing about 1682 daltons. Expression of the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) was shown, in Figure 1, to be decreased in Alzheimer's disease patients versus age-matched control patients, and thus, the claimed peptide is differentially expressed in Alzheimer's disease versus age-matched controls.

4. In order to further illustrate this point, Applicants provide the attached figure entitled "DEAE 3(Elution) AD vs. Age

Matched AD (Control)" which represents Figure 1 as originally filed. The attached figure was produced by scanning the original photograph of the gel. Increased expression of Band C1(lanes 5-8, especially lane 5, all samples obtained from patients age-matched to the Alzheimer's disease patients) versus Band C2(lanes 1-4, especially lane 1, all samples obtained from Alzheimer's disease patients) is evident in the figure. Thus, decreased expression of the claimed peptide in Alzheimer's disease is also clearly shown. No new matter has been added; this figure is simply a clearer copy of Figure 1 as originally filed and is provided to clarify the presence and differential expression of the claimed biopolymer marker (amino acid residues 2-14 of SEQ ID NO:1). The gel shown in the figure does not represent new experimentation; the figure shows a clearer image of the original gel made at the time that the experiments described in the instant specification were first carried out.

The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the Application or any patent issuing thereon.

11/30/2005
Date

Ferris H. Lander
Ferris H. Lander
Reg. No. 43,377

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Examiner copy
reference #1



1: J Neural Transm. 1996;103(4):433-46.



# Elevated 5-S-cysteinyldopamine/homovanillic acid ratio and reduced homovanillic acid in cerebrospinal fluid: possible markers for and potential insights into the pathoetiology of Parkinson's disease.

**Cheng FC, Kuo JS, Chia LG, Dryhurst G.**

Department of Medical Research and Geriatrics Medical Center, Taichung, Taiwan, Republic of China.

High-performance liquid chromatography with electrochemical detection has been employed to analyze ultrafiltrates of cerebrospinal fluid of Parkinson's Disease (PD) patients and age-matched controls for the dopamine (DA) metabolites homovanillic acid (HVA) and 5-S-cysteinyldopamine (5-S-CyS-DA). The mean level of HVA in the CSF of PD patients, measured 5 days after withdrawal from L-DOPA therapy, was significantly lower than that measured in controls. By contrast, mean levels of 5-S-CyS-DA were not significantly different in the CSF of PD patients taking L-DOPA (PD-LT patients) the same patients 5 days after discontinuing this drug (PD-LW patients) or controls. However, the mean 5-S-CyS-DA/HVA concentration ratio was significantly ($p < 0.05$) higher in the CSF of PD-LW patients compared to controls. Although the PD patient population employed in this study had been diagnosed with the disease several years previously and had been treated with L-DOPA for prolonged periods of time the results of this study suggest that low CSF levels of HVA and a high 5-S-CyS-DA/HVA ratio together might represent useful markers for early diagnosis of PD. The high 5-S-CyS-DA/HVA ratio observed in the CSF of PD-LW patients also provides support for the hypothesis that the translocation of glutathione or L-cysteine into neuromelanin-pigmented dopaminergic cell bodies in the substantia nigra might represent an early event in the pathogenesis of PD.

PMID: 9617787 [PubMed - indexed for MEDLINE]

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Nov 15 2005 04:49:13

2132.090 Examiner copy reference #2



1: Arch Neurol. 1999 Jun;56(6):673-80.



Comment in:

- Arch Neurol. 1999 Jun;56(6):655-6.



# Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease.

**Andreasen N, Hesse C, Davidsson P, Minthon L, Wallin A, Winblad B, Vanderstichele H, Vanmechelen E, Blennow K.**

Department of Rehabilitation, Pitea River Valley Hospital, Sweden. niels.andreasen@nll.se

OBJECTIVES: To study the diagnostic potential of the 42 amino acid form of beta-amyloid (beta-amyloid(1-42)) in cerebrospinal fluid (CSF) as a biochemical marker for Alzheimer disease (AD), the intra-individual biological variation of CSF-beta-amyloid(1-42) level in patients with AD, and the possible effects of differential binding between beta-amyloid and apolipoprotein E isoforms on CSF-beta-amyloid(1-42) levels. DESIGN: A 20-month prospective follow-up study. SETTING: Community population-based sample of consecutive patients with AD referred to the Pitea River Valley Hospital, Pitea, Sweden. PATIENTS: Fifty-three patients with AD (mean +/- SD age, 71.4 +/- 7.4 years) diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria and 21 healthy, age-matched (mean +/- SD age, 68.8 +/- 8.0 years) control subjects. MAIN OUTCOME MEASURES: Cerebrospinal fluid beta-amyloid(1-42) level--analyzed using enzyme-linked immunosorbent assay--and severity of dementia--analyzed using the Mini-Mental State Examination. RESULTS: Mean +/- SD levels of CSF-beta-amyloid(1-42) were decreased (P<.001) in patients with AD (709 +/- 304 pg/mL) compared with controls (1678 +/- 436 pg/mL). Most patients with AD (49 [92%] of 53 patients) had reduced levels (<1130 pg/mL). A highly significant correlation (r = 0.90; P<.001) between baseline and 1-year follow-up CSF-beta-amyloid(1-42) levels was

found. There were no significant correlations between CSF-beta-amyloid(1-42) level and duration (r = -0.16) or severity (r = -0.02) of dementia. Low levels were also found in patients with mild dementia (Mini-Mental State Examination score, >25). CONCLUSIONS: The sensitivity of CSF-beta-amyloid(1-42) level as a diagnostic marker for AD is high. The intra-individual biological variation in CSF-beta-amyloid(1-42) level is low. Low CSF-beta-amyloid(1-42) levels are also found in the earlier stages of dementia in patients with AD. These findings suggest that CSF-beta-amyloid(1-42) analyses may be of value in the clinical diagnosis of AD, especially in the early course of the disease, when drug therapy may have the greatest potential of being effective but clinical diagnosis is particularly difficult.

PMID: 10369305 [PubMed - indexed for MEDLINE]

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# Pharmacotherapy of Cognitive Impairment in Alzheimer's Disease: A Review

2132.090
Examiner copy
reference #3

Shirish V. Patel, MB, BS, MRCPsych

ABSTRACT

Experimental pharmacotherapy of cognitive impairment in Alzheimer's disease has seen a recent proliferation of drug trials involving a wide variety of drugs. Many of the earlier studies focused on cholinergic agents. However, subsequent advances in basic and biological sciences have broadened the scope of therapeutic strategies beyond the neurotransmitter approaches to include neurotrophic, metabolic-enhancing, membrane-modifying, and anti-toxic agents, and have also provided rationale for developing antiamyloid and anti-infective therapies. For the clinician, it has not been easy to keep abreast of these developments. In this article, I present an overview of the cognition-enhancing drugs that have been used in the past, of those currently under investigation, and of new drugs and strategies that are likely to receive attention in the next few years. (*J Geriatr Psychiatry Neurol* 1995; 8:81–95).

One in nine Americans is now aged 65 years or older, a figure projected to double by the middle of the next century. Approximately 10% of this older generation have probable Alzheimer's disease (AD).[1] The fourth leading cause of death in the United States after heart disease, cancer, and stroke, AD accounts for the occupancy of half of all nursing home beds. At present, management of AD encompasses the use of medications, education and support of both the patient and caregivers, prompt treatment of comorbid events, maintenance of safety, and provision of optimal levels of social, physical, and psychological stimulation.[2]

The focus of this piece is the experimental pharmacotherapy used both for the cognitive changes related to AD as well as for slowing or halting the progression of the illness. Pharmacotherapy of behavioral, affective, and psychotic symptoms is important as well, but will not be reviewed here.

To date, there is neither a clear understanding of the origin and pathophysiology of AD nor an animal model of the illness. Since patients, families, professional caregivers, and the health care system are faced with rapidly increasing numbers of victims, there has been considerable demand to offer relief from this debilitating disease. In view of this pressure, there has been a large number of therapeutic trials over the last 30 years.

Some trials are derived from basic scientific principles or advances, others are derived from serendipitous observations, some come from retrospective naturalistic studies, and some are frankly empirical. No single approach has led to a breakthrough, although there are leads that offer both more and less promise.[3] In many instances, it can be hard to judge either the scientific underpinnings or the significance of clinical trials. It has not been easy for the clinician to keep abreast of the progress or problems in the field. This difficulty will intensify in the coming years, as both the rate of trials and the rate of scientific discovery increase.

The primary purpose of this paper is to present a logical framework for simplifying and categorizing this potpourri of clinical experience. Therapeutic agents that have been studied, those currently under study, and new drugs and strategies will be presented according to this framework, summarized in Table 1. The organizing principles for the framework are the neurochemical properties of the agents and their known or postulated mechanisms of action. For each general class of drugs, the rationale, aims, results, present state and possible future role in the treatment of AD are discussed.

Certain housekeeping details need to be addressed at the outset. The term, dementia of the Alzheimer type (DAT), refers to the clinical syndrome of impaired intellect, memory, and personality, while the term, Alzheimer's disease, refers to a combination of the characteristic clinical syndrome and the associated histopathologic findings of plaques and tangles in appropriate areas of

Received July 10, 1992. Received revised October 20, 1993. Accepted for publication November 4, 1993.

From the Department of Psychiatry, University of Rochester School of Medicine and Dentistry, and the Psychiatry Unit, Monroe Community Hospital, Rochester, New York.

Reprint requests: Dr. Shirish V. Patel, Department of Psychiatry, Monroe Community Hospital, 435 E. Henrietta Road, Rochester, NY 14620.



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Table 1. Summary of Strategies

1. Neurotransmitter-based
   a.) acetylcholine
   b.) catecholamines
   c.) serotonin
   d.) GABA, glutamate
   e.) peptides
2. Neurotrophic
3. Metabolic-enhancement
4. Membrane modification
5. Amyloid
6. Toxic
7. Vascular
8. Infectious
9. Miscellaneous
10. Future
    a.) specific cholinergic agonist/antagonist
    b.) neurotransmitter "cocktail"
    c.) agents to alter amyloid metabolism
    d.) antiexcitotoxic
    e.) agents to alter mitochrondrial metabolism

the brain. Over the years, many sets of diagnostic criteria for the clinical diagnosis of AD have been developed and refined, with the result that the diagnostic accuracy of AD has increased significantly. Today, the two most widely used clinical diagnostic criteria are those developed by the NINCDS-ADRDA Work Group[4] and the DSM III-R Work Group.[5] Since these criteria were formulated only in the last 10 years, those used in many of the earlier drug studies of AD will have been lax by comparison. These earlier studies likely will have included patients with dementia other than that of the Alzheimer type, which will have, of course, affected their results. In the following article, the studies that have used acceptable diagnostic criteria and those that have been based on sound rationales are discussed in some detail, while studies that have used less rigid diagnostic criteria and those based on empirical rationales are touched upon only briefly. Finally, for the purposes of this review, the term, cognition, is used operationally to include the domains of attention, memory, language, visuospatial functions, and psychomotor speed, and the outcome measures are discussed in these contexts.

## I. NEUROTRANSMITTER-BASED STRATEGIES

Neurotransmitters are neuroactive agents involved in synaptic transmission. Changes in their concentrations in the brain are believed to play an important role in the pathophysiology of behavioral and cognitive changes seen in AD. Neurotransmitter-based therapeutic approaches aim to correct neurotransmitter deficits using various strategies including (1) increasing neurotransmitter synthesis, by providing precursor substances (precursor loading); (2) inhibiting neurotransmitter breakdown (metabolic enzyme inhibition); (3) facilitating neurotransmission, by administering substances that will act upon specific receptors (agonist administration); and (4) combining two or more of the above strategies. These strategies are exemplified by the systematic manipulation of the central cholinergic neurotransmitter system to enhance cognitive abilities in patients with DAT, also the approach most frequently used in the last decade.

### A. Cholinergic Drugs

There is substantial evidence pointing to both a widespread disruption of the central cholinergic neurotransmitter system in AD as well as the association of these changes with cognitive impairment. For example, brains of patients with AD show marked reduction in the activity of choline acetyltransferase (ChAT),[6–8] an enzyme important in the synthesis of acetylcholine (ACh); reduced levels of ACh[6,9]; reduced activity of acetylcholinesterase (AChE),[10] the catabolic enzyme for ACh; and reduced high-affinity choline uptake (HACU).[11] Reduced brain ChAT activity, both antemortem[12] and postmortem[6] correlates with the degree of cognitive deficit exhibited. ChAT activity also correlates inversely with senile plaque[8] and neurofibrillary tangle counts,[13] and in turn, the latter two correlate with severity of the dementia.[13,14] Studies of brains of patients with AD have also demonstrated a significant loss of neurons in the Meynert nucleus,[13] a major source of cholinergic neurons; regional reductions in density of both muscarinic[15] and nicotinic receptors[16]; and the presence of cholingeric neurons in senile plaques.[17] Significant AChE activity has been demonstrated in plaques and tangles.[18] These changes are most evident in the cerebral cortex and hippocampus, which are areas also believed to be important in normal cognition. Finally, pharmacologic studies have shown that when scopolamine, an anticholinergic drug, is administered to normal healthy subjects, it produces cognitive changes similar to some of those seen in DAT.[19]

These neurochemical, histopathologic, and neuropharmacologic findings form the basis of the so-called "cholinergic hypothesis" of dementia in AD.[20,21] Briefly, this hypothesis attempts to attribute the cognitive changes occurring in AD to a deficiency of ACh in certain parts of the brain. Based on these premises, the general aim of the cholinergic strategies has been to enhance central cholinergic neurotransmission by increasing either presynaptic release of ACh or postsynaptic response to ACh.

#### *ACh Precursors*

The precursors of ACh, lecithin and choline, have been administered to DAT patients with the aim of correcting the presumed presynaptic deficiency of ACh. Neither lecithin[22–24] nor choline[25,26] has produced any significant effects administered alone. This may be due to a number of factors. Synthesis of ACh requires an acetyl group donor in addition to choline; therefore, administration

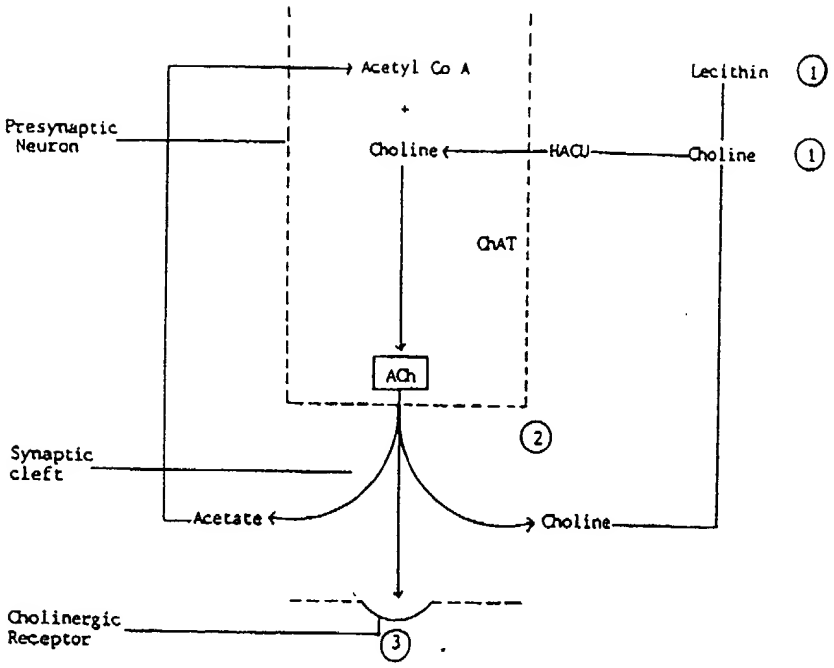


Figure 1. A diagram of the synthesis and metabolism of acetylcholine (ACh) is shown.
*Numerals indicate sites of therapeutic approaches: 1 = Precursor loading; 2 = Metabolic enzyme inhibition; 3 = Agonist administration.
Acetyl CoA = acetylcoenzyme A; ChAT = choline acetyltransferase; AChE = acetylcholinesterase; HACU = high affinity choline uptake.

of choline may not be sufficient to augment brain ACh levels. It is also possible that neither precursor is able to reach the brain in sufficient quantities to be effective. Consequently, augmentation strategies combining lecithin with AChE inhibitors have been tried with the aim of prolonging the effect of ACh in the synapse. Short-term administration of the combination of lecithin and physostigmine to small groups of patients has resulted in an improvement in measures of long-term memory in some patients.[27,28] Improvement in verbal learning sustained for several months was reported with chronic administration of this combination in one small sample,[29] although other investigators were not able to replicate this finding.[30] Another augmentation study combining lecithin with pilocarpine[31] was ineffective in two patients with DAT.

The release of ACh into the synapse is an important aspect of enhanced cholinergic neurotransmission. Cholinergic transmission is not enhanced by simple increased synthesis of ACh in the presynaptic neuron, although augmentation does occur by increased release of ACh (which also leads to increased ACh synthesis). This coupling between ACh release and synthesis is believed to be mediated by HACU. Piracetam (see below), a compound believed to increase ACh release, therefore, was combined with lecithin[32] and choline,[33] but the results were negative.

In summary, precursor loading, on its own or in rational combination with other drugs that augment its actions, have failed to produce consistent results so far. Other potential augmentation strategies, such as combination of a precursor loading agent and an acetyl donor drug, require further exploration.

### *AChE Inhibitors*

Physostigmine is the drug most commonly studied in this category. A reversible inhibitor of AChE, it has a half-life of 15 to 30 minutes. It is rapidly absorbed after oral administration and readily enters the brain, where its diffusion is widespread because of its lipophilic quality. Numerous studies have examined the effects of this drug on cognition in DAT patients. A simple comparison of the studies is not possible, as there is wide variation in the dose, frequency, routes, and duration of administration of the drug, and especially in the cognitive memory paradigms studied. The results have ranged from dose-dependent, statistically significant improvements in attention, short- and long-term memory,[34] mild improvement in picture recognition,[35] and modest improvement in constructional ability,[36] to no effect at all.[37]

Discrepancies between the various physostigmine studies may be due to several factors. Dose-response studies of physostigmine have yielded an inverted U-shaped curve, suggesting that efficacy studies of physostigmine may require individually tailored dosages. Multiple dosing may be necessary, because physostigmine has a very short half-life. It also has significant side effects, some of which may mask the positive effects of the drug. The temporal relationship between AChE inhibition and changes in behavior may be an important factor, something that will be better understood as sensitive and reliable means of assaying plasma physostigmine levels become available.

The positive findings in the above studies might be of clinical significance if it can be shown that the changes can be sustained, and if improved performance on sophisticated psychometric tests correlate with meaningful improvements in patients' activities of daily living. Unfortunately, there have been only a few studies examining the effects of chronic administration of physostigmine on cognition, and the results have been equivocal. In a 12-week, double-blind, placebo-controlled, pilot study of 16 patients with DAT, Thal et al[38] reported improvement in verbal memory, specifically retrieval from long-term storage, in seven of 10 patients who received the drug. This improvement was found to be marked in two patients and mild in five. The patients were also rated by their family members, who indicated mild to moderate improvement in both memory and performance in activities of daily living in six of the seven patients who showed improvement on psychometric testing. Jotkowitz,[37] however, did not find any improvement after 10 months of treatment in a single-blind, crossover trial of 10 patients with DAT.

Attempts to overcome some of the limitations associated with physostigmine use have resulted in the development of the so-called "second- and third-generation" AChE inhibitors including metrifonate, huperzine, and heptyl-physostigmine. Compared to physostigmine, these are less toxic and have longer durations of action. Preliminary data from studies using these drugs look encouraging.[39,40] On the other hand, one-time use of the longer acting pyridostigmine (with a half-life of 90 to 120 minutes) did not bring about any significant improvement in measures of cognitive functions in a small sample of patients with DAT.[41]

No other cognition-enhancing drug in the pharmacotherapy of DAT has generated as much interest and controversy in the last decade as tetrahydroaminoacridine (THA). THA is a long-acting (half-life of 80 minutes), reversible, cholinesterase inhibitor whose other postulated mechanisms of action include blockade of potassium channels, with consequent enhanced ACh release; direct effects on nicotinic and muscarinic receptors, resulting in increased synaptic cholingeric activity; inhibition of monoamine oxidase (MAO), with possible increase in monoaminergic transmitter levels[42]; and reversal of defective cell membrane, protein-protein interactions.[43] The side effects most commonly associated with this drug include hepatotoxicity, with asymptomatic elevation of liver enzymes, particularly the transaminases; autonomic disturbances, including nausea, vomiting, diarrhea, abdominal discomfort, and diaphoresis; and muscle stiffness. Some studies have reported up to 80% of their patients experiencing one or more of these troublesome side effects.[44]

THA achieved prominence after Summers et al[45] reported "dramatic improvement" in 17 patients with moderate to severe DAT. This study, however, was considered flawed,[46,47] with the result that the findings were difficult to interpret. Some beneficial effects, however, have been reported by others, including studies in which THA was combined with lecithin. In a double-blind, placebo-controlled, crossover trial of 52 patients, a small but statistically significant improvement in Mini-Mental State Examination (MMSE)[48] score was found after 4 weeks of treatment.[49] In a 13-week study of 65 patients with mild to moderate DAT, Eagger et al[50] also found improvement of three or more points on the MMSE. These investigators suggested that THA actually slowed the progression of the illness, a conclusion which has been questioned.[51] A multicenter study of 67 patients, however, was unable to demonstrate any improvement in cognition with either short- or long-term use of this drug combination.[52a]

Two double-blind, placebo-controlled, parallel-group, multicenter studies reported on the safety and efficacy of THA in patients with mild to moderate DAT. Davis et al[52b] reported a statistically significant, but not clinically evident, reduction in the decline of cognitive functions in the THA group in a 6-week study of 215 patients. This cohort was selected on the basis of a favorable response to THA from an original group of 632 subjects, all of whom received an optimum dosage of the drug for 6 weeks. In the other study of 468 patients over a 12-week period, Farlow et al[52c] reported a dose-related improvement in some patients in their performance on cognitive tests and in clinician-rated, clinical global improvement of change. Only 58% of the enrolled subjects completed the trial, however. In each study, more than 40% of the subjects had reversible elevation of the liver enzyme alanine aminotransferase.

In the summer of 1993, the Food and Drug Administration approved the use of THA in patients with DAT. In prescribing this drug, clinicians will be faced with issues such as which patients should receive the drug and at what degree of liver toxicity should the drug be discontinued.

### *Receptor Agonists*

A third strategy aimed at enhancing central cholinergic neurotransmission in patients with DAT has been to use drugs that act directly on cholinergic receptors. There are two types of cholinergic receptors that can be differentiated pharmacologically: muscarinic and nicotinic. At least five subtypes of muscarinic receptors, designated M1 to M5, have been discerned using molecular techniques. Stimulation of M2 receptors, which are located at the presynaptic neuronal terminals, inhibits ACh release, while stimulation of M1 receptors, located at postsynaptic neuronal terminals, results in enhanced release of ACh into the synapse. In AD, there is approximately a 20% reduction in muscarinic-receptor binding in the cerebral cortex, and this is believed to be primarily due to a loss of M2 receptors.[15] Significant regional reduction in the density of nicotinic receptors compared to normal controls has also been reported.[16] These findings

suggest that receptor-specific cholinergic agonists may have utility in AD, but unfortunately, the data available are largely from nonspecific agents: the ultimate potential of this strategy remains unproven.

Arecoline, a naturally occurring alkaloid, is a relatively selective, muscarinic-receptor agonist when used in low doses with probably nonspecific, pre- and postsynaptic effects. Slightly improved picture recognition[35,53] and enhanced word-finding ability, along with psychomotor activation and improved affect,[53] have been reported with intravenous infusions of low dosages of this drug. Likewise, a pilot study of intravenous nicotine showed very modest cognitive effects.[54] Other muscarinic-receptor agonists, including RS86,[55] pilocarpine,[31] and oxotremorine[56] have been generally ineffective.

Intracerebroventricular administration of agonists has been attempted to eliminate systemic side effects and peripheral inactivation of the drug, and to optimize the delivery of the drug to the brain. Intracerebroventricular administration of bethanechol chloride produced modest but clinically insignificant improvement in the MMSE scores of 49 patients with biopsy-proven AD in one study,[57] but only mild affective and behavioral improvements, without any cognitive effects, in another study of 10 patients.[58] These studies, however, demonstrated the feasibility and relative safety of using this particular route of administration.

Studies of a more selective M2-receptor blocker, aminopyridine, yielded conflicting results.[59,60] Aminopyridine causes an increased release of ACh from the neuron. It does so by blocking the cellular potassium channels, which results in prolongation of the neuronal action potential. Further evaluation of this drug and its vastly more potent analog, 3–4 diaminopyridine, is merited. Attempts are underway to develop highly selective, M1-receptor agonists, and animal data on one such drug, AF102 B. look promising.[61]

In summary, despite ample evidence implicating the central cholinergic neurotransmitter system in the pathophysiology of dementia of AD, the use of cholinergic drugs to improve cognition in these patients has brought about only slight improvement thus far. This may be so, in part, because other neurotransmitter systems are also disrupted in AD, and therefore, correction of a single neurotransmitter deficit may not be sufficient in itself to bring about a reversal of the cognitive changes; the cholinergic deficit may result from a primary cortical insult; the cholinergic deficit may be reversible only in the early stages of the illness; the cholinergic agonists tried so far may not have been the "right" ones, since some of the agonists used presumably have nonspecific and, therefore, opposing receptor effects (contrasted with the profound and uniform effects of antagonists[19]; or because a clinically homogenous, patient population may not necessarily be a neurochemically homogenous group. However, the fact that some cholinergic drugs have been able to enhance cognition at all underlines the significance of the cholinergic system in cognition and offers continued hope that more specific cholinergic therapies may yet be beneficial.

### B. Catecholaminergic Drugs

The overall principles of neurotransmission described for the cholinergic system pertain to other systems as well. For instance, tyrosine is converted to L-DOPA, then to dopamine, and ultimately, by dopamine beta hydroxylase, to norepinephrine. Monoamine oxidase, which exists in two forms (A and B), catabolizes dopamine and norepinephrine.

Evidence that catecholaminergic systems are also disrupted in brains of AD patients includes a demonstration of loss of neurons from locus ceruleus,[62] the origin of nonadrenergic innervation of the cerebral cortex and hippocampus; reduced level of noradrenaline in these areas of the brain[63]; and reduced activity of dopamine beta hydroxylase,[64] the specific biosynthetic marker enzyme of noradrenaline. Finally, levels of MAO-B are increased in AD,[63,65] suggesting the possibility that some of the symptoms of DAT may be the result of reduced functional neurotransmission of MAO-B substrates. Unlike the cholinergic neurotransmitter system, however, correlations between catecholaminergic biochemical parameters and neuropathologic changes have not been robust.[66]

The strategies used to enhance central catecholaminergic transmission are similar to those used with

Table 2. Catecholaminergic Therapeutic Studies in DAT

| *Strategy* | *Drug* | *Selected References* |
|---|---|---|
| I. Precursor loading | tyrosine | Kushnir et al[159] |
| | levodopa | Kristensen et al[160] |
| II. Metabolic enzyme inhibition | l-deprenyl | Tariot et al[67] |
| | tranylcypromine | Tariot et al[161] |
| III. Agonist administration | clonidine | Mohr et al[162] |
| | guanfacine | Schlegal et al[163] |
| | amantidine | Schubert et al[164] |
| | bromocriptine | Phuapradit et al[165] |
| | memantine | Fleischacker et al[166] |

Table 3. Serotonergic Therapeutic Trials in AD

| *Strategy* | *Drug* | *Selected References* |
|---|---|---|
| I. Precursor loading | tryptophan | Smith et al[167] |
| II. Metabolic enzyme inhibition | tranylcypromine | Tariot et al[161] |
| III. Agonist administration | alapractolate | Dehlin et al[77] |
| | zimeldine | Cutler et al[168] |
| | trazodone | Greenwald et al[76] |
| | M-CPP | Lawlor et al[78] |
| | citalopram | Nyth et al[75] |

cholinergic drugs (Table 2). The cognition-enhancing effects of the catecholaminergic drugs in DAT patients have been largely negative, with the possible exception of L-deprenyl (selegiline HCl). L-deprenyl relatively selectively inhibits MAO-B at low doses and has few side effects, with the result that it is generally well tolerated. In a preliminary study of 17 patients with DAT, it produced improvement in a memory and learning task that required complex information processing and sustained effort.[67] Associated behavioral changes included increased energy and social interaction and decreased anxiety and depressed mood, which may indeed have been the primary effect of the drug. Statistically significant improvements in measures of memory and attention, following prolonged administration of L-deprenyl over 3 months, have been reported by several investigators.[68–71] This particular strategy and agent probably warrant more detailed study.

### C. Serotonergic Drugs

Brains of patients with AD show cellular loss and a preponderance of neurofibrillary tangles in the dorsal raphe nucleus,[72] a major source of serotonergic neurons projecting to the cerebral cortex and hippocampus. In the cerebral cortex, concentrations of 5HT and its metabolite 5HIAA are reduced,[73] and 5HT-receptor numbers are decreased[74]: the only receptors consistently found to be reduced in AD. Table 3 lists drugs used to augment brain 5HT levels employing strategies similar to those used in enhancing central cholinergic and catecholaminergic neurotransmission. Significant behavioral improvements have been reported with citalopram, which bears pursuing, and there are reports of improvement in disturbed behavior with trazodone.[75,76] However, a significant cognitive effect of these drugs and others in this class, including alapractolate[77] and m-chlorphenylpiperazine (M-CPP),[78] is lacking.

### D. Other Aminergic Drugs

As evidence of deficiency of other neurotransmitters in AD is emerging, attempts are being made to augment their brain levels as well. However, early attempts to correct glutamatergic and GABAergic deficiencies, using milacemide[79] and tetraisoazolopyridine (THIP)[80] respectively, have not yielded positive clinical results. Likewise, imipramine[81] and minaprine,[82] which facilitate actions of multiple neurotransmitters including 5HT, dopamine, and ACh, have failed to demonstrate any specific antiamnesic effect in patients with DAT.

### E. Peptidergic Therapies

Neuropeptide restitutive therapies have been based on the premises of the biogenic amine treatments described above. The concentration of somatostatin (SRIF) in the cerebral cortex and cerebrospinal fluid (CSF) has been frequently shown to be reduced in AD,[83–85] and its presence has been demonstrated in both neuritic plaques[86] and neurofibrillary tangles.[87] Parenteral administration of a potent analog of somatostatin to a small sample of patients with DAT was without benefit, however.[88]

Adrenocorticotropic hormone (ACTH) is believed to be important in maintaining central cholinergic and catecholaminergic activities.[89,90] The reduced brain levels of ACTH in AD may account, therefore, for reduced levels of ACh and catecholamines. Animal studies have demonstrated that analogs of ACTH improve memory in senescent monkeys.[91] In view of these findings, synthetic ACTH analogs were administered to patients with DAT, but with neither cognitive improvement[92] nor any biochemical interaction with the neurotransmitter systems believed to be involved in AD.[93]

The facilitatory effect of arginine vasopressin (AVP) on learning and memory in animals[91] and evidence of its depletion in subcortical areas[94] and CSF[95] in AD have led to its use in dementia. A small, statistically significant improvement in certain noncognitive behaviors was reported in a small group of DAT patients,[96] but a much larger and longer study was unable to demonstrate any benefit.[97]

In animals, thyrotropin-releasing hormone (TRH) exerts a positive neuromodulatory effect on the cholinergic system,[98] presumably by enhancing both ACh synthesis and release, and by increasing the sensitivity of M1 receptors to ACh. In man, TRH attenuates scopolamine-induced impairment of memory.[99] Moreover, its ability to cross the blood-brain barrier readily, because it is only a tripeptide, makes it a suitable agent for antiamnesic therapy in cases where the cholinergic system is disrupted, as in the case of DAT. In preliminary infusion studies in patients with DAT, TRH produced modest improvement in arousal and semantic memory when administered on its own,[100] and in measures of both verbal and visual memories when coadministered with lecithin.[101] These studies also demonstrated the relative safety of TRH administration in patients with DAT.

Gonadal hormones influence brain development and function during normal growth. In an open study of estrogen in 7 postmenopausal women with DAT, slight improvement in MMSE scores were reported.[102] However, this may have been secondary to estrogen's positive effect on emotional factors, which are known to modulate memory and learning. Due to the high risks of endometrial cancer and thromboembolic phenomena, particularly in elderly woman, more controlled trials would be necessary to establish the safety and efficacy of estrogen in DAT.

The rationale for the use of opioid antagonists as cognition-enhancing agents in DAT patients was based upon the hypothesis that dystonic overactivity of the opioid system inhibits GABAergic systems, which in turn disinhibit other neurotransmitter systems including the cholinergic neurotransmitter system. Administration of

naloxone,[103,104] a centrally acting, competitive, opioid-receptor antagonist, devoid of any agonist activity, as well as naltrexone[105] and nalmefene,[106] however, all yielded negative results.

From the foregoing account of neurotransmitter-based strategies in the treatment of DAT, it is clear that functional augmentation of any one neurotransmitter system in isolation from other neurotransmitters has failed to produce significant cognitive improvement. Future neurotransmitter-augmentation strategies may need to use more selective agents and possibly to impinge on multiple-neurotransmitter systems in a "cocktail" approach.

## II. NEUROTROPHIC-BASED STRATEGIES

Most central nervous system (CNS) growth occurs during development. The adult CNS retains mechanisms for maintenance and repair that include factors called neurotrophic factors, an example of which is nerve growth factor (NGF) (see below). Neurotrophic factors are believed to play a regulatory role in neuronal-cell survival, neuritic growth, and synaptic formation. Deficiency or decreased availability of these neurotrophic factors in neurodegenerative disorders like AD are believed to cause mechanical failure, with the result that neurons get weak and eventually degenerate. Direct evidence of reduced trophic activity as a cause of neurodegenerative disorders is lacking, although there is some circumstantial evidence.

The rationale for using GM1-monosialoganglioside (GM1) in DAT is based on the findings that the brain ganglioside content of patients with dementia is significantly less than that of controls,[73] and that, in experimental animals, GM1 promotes neuritogenesis[107] and has a neuroprotective effect against certain toxins. It acts synergistically with other neurotrophic factors and is not, therefore, a growth-promoting factor in its own right. In a 12-week pilot study of 46 patients with DAT, however, GM1 did not produce any significant change in measures of cognitive functions.[108] These patients tolerated the drug well, leaving scope for studying the effects of higher dosages for longer durations.

Another neurotrophic agent that has stirred excitement is nerve growth factor (NGF). A polypeptide secreted by astroglia, NGF acts on both neuronal and non-neuronal cells. It regulates neuronal growth by increasing the diameter of the neuronal cell, arborization of its axon, density of its synaptic connections, and the quantity of neurotransmitter it produces.[109,110] NGF receptors on forebrain cholinergic neurons have been demonstrated in AD.[111] Additionally, animal studies of mammalian brains have shown that receptors for NGF are present on the cholinergic neurons of the forebrain where the peptide exerts trophic effects, including increased axonal sprouting and production of ChAT.[112,113] Based on these data, the hope is that exogenous administration of NGF to AD patients would enhance central cholinergic neurotransmission and prevent forebrain cholinergic neuronal death.[114] Human trials with NGF will not be conducted until considerable preclinical study is performed.

## III. METABOLIC ENHANCERS

In DAT, there is diminished glucose utilization and abnormal oxidative metabolism in certain parts of the brain. Drugs have been used with the specific aim of correcting these abnormalities by enhancing the metabolic activity of the brain. These so-called metabolic enhancers can be classified broadly into three groups: ergot alkaloids, nootropics, and vinca alkaloids.

Ergot alkaloids are widely prescribed drugs for the symptomatic treatment of dementia, and co-dergocrine mesylate (hydergine), a mixture of three dihydrogenated alkaloids, is the best studied. It is also the only FDA-approved drug for treatment of dementia, for which it has been in use for more than 30 years. At first, co-dergocrine was used as a putative vasodilator. Later, when it was demonstrated that patients with DAT do not have reduced cerebral blood flow, the rationale for the continued use of the drug appears to have become more empirical. Reasons for its sustained popularity in the pharmacotherapy of DAT include the lack of a universally effective treatment for DAT; the findings of behavioral improvements (particularly affect), albeit small, in several studies[115,116]; the demonstration of its relative safety, even with long-term use[117]; and the anecdotal reports of dramatic improvement in an occasional patient.[116] Reviews of the extensive clinical trials of co-dergocrine in dementia fail, in general, to produce a clear consensus on the efficacy of this drug as a cognition-enhancing agent, however.[118–120] With reference to DAT, a well-designed, double-blind, placebo-controlled study of 80 patients who were treated with the conventional dose of 3 mg/daily for 6 months, failed to demonstrate any cognitive improvement.[121]

However, another study of 41 mildly impaired patients using a dose of 6 mg/daily reported an improvement of more than 20% in short-term memory, sustained for 12 weeks with treatment.[122] These results need confirmation, preferably using more-refined outcome measures. Results from long-term treatment studies[123] have shifted the focus of co-dergocrine use from baseline improvement in cognition to forestalling intellectual decline in DAT patients. There may be some merit in pursuing this strategy, as studies in aged rodents have demonstrated a modulating effect of co-dergocrine on morphologic plasticity of the synaptic junction.[124] Studies addressing this issue and using almost three to four times the conventional dose of 3 mg per day, are currently underway. Hopefully, the outcome of these trials should clarify the position of this rather expensive drug in the treatment of DAT. The fact that it is "approved" is partially an historical phenomenon, and should not lead to the presumption that clinically meaningful efficacy has been established.

One other ergot derivative, nicergoline, was reported to reduce disorientation in about 30% of patients with "mild-to-moderate dementia" in a large multicenter study.[125] Its efficacy in patients with DAT, however, requires confirmation.

Nootropics (Noos = mind; tropein = towards) represent the second class of drugs with putative, brain, metabolic-enhancing effects that has been tried in the treatment of dementia for over 20 years. Biochemical actions of these drugs, based on animal studies, include enhancement of dopamine release[126] and possible facilitation of cholinergic neurotransmission.[127] This latter action is believed to be affected by enhancing HACU, the rate-limiting step in ACh synthesis (Figure 1), which in turn leads to increased ACh synthesis and release. In experimentally impaired animal brains, nootropics increase both cerebral blood flow and CNS metabolism, and animals show improvements in measures of short-term memory.[127] These animal data, together with the ability of nootropics to antagonize scopolamine-induced amnesia,[128] formed the rational basis for study of this class of drugs in patients with DAT. Unfortunately, the results of clinical trials, on the whole, have been disappointing. Piracetam, a prototype nootropic, failed to produce any cognitive improvement in a double-blind, crossover trial in DAT patients.[129] Similarly, other nootropics including aniracetam[130] and oxiracetam,[131] the most recently developed drug in its class, failed to show any significant positive cognitive effect.

The third group of metabolic enhancers is the vinca alkaloids. Vinpocetine, a synthetic vinca alkaloid, has neuroprotective and cognition-enhancing effects in animals.[132] In DAT patients, it failed to improve cognition, even after prolonged administration.[133]

These negative findings with metabolic enhancers are not totally surprising. The animal studies that have provided the rationale for the use of these drugs in humans have generally used brains that were experimentally impaired by either hemorrhagic hypotension or hypoxia, factors not believed to be important in the pathogenesis of AD. Furthermore, most of the animal data have been collected from studies of rodents, with limited ability for generalization to humans.

## IV. MEMBRANE MODIFYING AGENTS

The dendritic tree and its spines, which play an important role in signal transmission, undergo morphologic modification according to synaptic input. With age, dendritic arborization and spines of some pyramidal cells undergo progressive degeneration; these losses are exaggerated in AD.[134] These changes may be secondary to reduced synaptic input and/or alteration in the membrane structure of the affected pyramidal cells, especially age-dependent increases in membrane cholesterol.[135] These membranal changes may lead to a functional impairment of cerebral functions such as learning and memory. A further postulate is that the changes in membrane properties alter the release of, and response to, ACh, which might be related to degeneration of cholinergic neurons in AD. Based on this thinking, agents that would reverse changes in membrane fluidity and cholesterol content, and enhance cholinergic transmission, have been studied in patients with DAT.

Phosphatidylserine, a phospholipid naturally present in the biochemical membrane, increases both membrane fluidity and turnover of several neurotransmitters, particularly ACh, in the brain. In a multicenter trial of patients with DAT, phosphatidylserine produced slight improvement in several domains, including concentration, memory, and activities of daily living.[136] Interestingly, these improvements were more evident in the most severely impaired patients and were sustained for 6 months while the patients remained on the treatment. Patients who were on placebo showed significant deterioration over the same period of time. These preliminary findings have raised the possibility that phosphatidylserine may have a prophylactic effect and may modify the clinical course of the illness. A long-term treatment study of a larger group of patients is required to confirm these findings.

By way of contrast, S-adenosyl-1-methionine, another membrane modifying agent, did not produce any positive results in four DAT patients.[137]

## V. ANTIAMYLOID STRATEGIES

The three pathologic hallmarks of AD are neuritic plaques, neurofibrillary tangles, and vascular amyloid: all containing amyloid proteins. Their major component is called beta amyloid, derived from cleavage of an apparently normal, precursor protein. These insoluble proteins accumulate extracellularly as well as intracellulary in AD, possibly because of ineffective cleavage. Extracellular deposition of amyloid in its association with neuritic plaques is believed to interfere with synaptic transmission and may be toxic to the neurons.[138] Intracellular-amyloid accumulation in the form of neurofibrillary tangles may also play a role in neuronal death,[139] although it is not yet certain whether amyloid is actually toxic, trophic, or merely "debris." Moreover, the density of plaques and tangles is highest in the hippocampus and neocortex, areas of the brain believed to be important in normal cognition, as mentioned above. The inference is that deposition of amyloid in the brains of AD patients may contribute to the cognitive impairment seen in the illness. Therapeutic approaches aimed at preventing amyloidogenesis and amyloid deposition by restoring the function of the protease responsible for cleavage of the precursor protein, for example, could be potentially useful.[140]

## VI. ANTITOXIC THERAPIES

Use of chelating agents, drugs that form soluble complexes with metals, in the treatment of DAT is based upon several rationales.[141,142] Some studies have demonstrated elevated levels of aluminum in the brains of AD patients.[143,144] This elevation is particularly evident in the neocortical areas, which also show a high density of neurofibrillary tangles. Several epidemiologic studies have reported an increased incidence of senile dementia in geographic areas with high aluminum content in the drinking water.[145,146] In a 2-year, open study of patients with DAT, desferrioxamine, a chelating agent with high affinities for aluminum and iron, produced a significant reduction in the rate of decline of activities of daily living compared to the placebo group.[147] Changes in cognitive measures could not be compared, as most of the patients were unable to complete the tests. The authors concluded that chronic administration of desferrioxamine may slow the progression of the illness. Reduced brain aluminum levels has also been reported in a postmortem study of 4 patients with AD treated with the drug.[141] Whether there was any concomitant improvement in cognition during the treatment period is not known. Another chelating agent, ethylenediaminetetraacetic acid (EDTA), was shown to be ineffective and to cause significant renal and cardiovascular toxicity.[148]

Whether aluminum accumulation in the brain of AD patients is a passive phenomenon related to aging[149] or a pathogenetic factor is unknown, since elevated brain aluminum level in AD has not been demonstrated unequivocally. Until more information is available, extreme caution is appropriate in advocating the use of this very costly and perilous mode of treatment for DAT patients.

Further suggestion of an environmental toxin as a causative factor for AD comes from the study of Guam Amyotrophic Lateral Sclerosis-Parkinsonism-Dementia Complex (Guam ALS/PDC). This neurodegenerative disorder, which bears neuropathologic similarities with AD,[150] is seen in epidemic proportions in the Chamorro indigenes of the Western Pacific island of Guam. Preliminary studies suggest that the toxin responsible may be an amino acid present in the fruit of the false sago palm and used as food and medicine by the affected population, since monkeys fed chronically on the fruit developed clinical symptoms and neuropathologic features similar to the Guam ALS/PDC. Confirmation of these observations should aid the development of potential antitoxin therapy.

Another antitoxic therapeutic approach involves calcium channel-blocking drugs. Calcium ions, believed to be toxic to hypoxic neurons,[151] have been implicated in the neuronal cytoskeletal disruption and neurofibrillary-tangle formation seen in AD.[152,153] Also, increased concentrations of calcium has been demonstrated in tangle-bearing neurons.[154] Based on these rationales, calcium channel-blocking drugs have been studied in patients with DAT with the aim of blocking the entry of calcium ions into the neurons causing further injury. Nimodipine, a calcium channel-blocker with predilection for cerebral vasculature, produced modest improvement in measures of long-term memory and activities of daily living in a preliminary study of 227 patients.[155] A longer term treatment protocol by these investigators is in progress.

## VII. VASCULAR AGENTS

Vascular agents that have been tried, but that have produced negative results, are listed in Table 4. These drugs were originally prescribed because it was believed that cognitive impairment in dementia resulted from reduced cerebral blood flow and, consequently, reduced tissue oxidation. It is now known that decreased cerebral blood flow follows the onset of symptoms in DAT and is probably a consequence of reduced neuronal activity.[156]

## VIII. ANTI-INFECTIVE STRATEGIES

The hypothesis that AD may result from a viral infection is based on the belief that transmissible dementing illnesses, like Creutzfeldt-Jakob disease and Kuru, are caused by "slow viruses." However, the failure either to transmit AD to nonhuman primates or to identify any potential transmissible agent has hitherto precluded development of any anti-infective treatment.[157a,b]

## IX. MISCELLANEOUS THERAPIES

Table 5 lists some of the other cognition-enhancing drugs that have been used in DAT patients. The results, on the whole, have been negative. Epidemiologic review of patients with AD and with rheumatoid arthritis suggested a reduced prevalence of AD in the arthritis group.

Table 4. Some Vascular Agents Studied in Dementia

| *Strategy* | *Drug* | *Selected References* |
|---|---|---|
| I. Vasodilation | cinnarizine | Bernard et al[169] |
| | cyclandelate | Capote et al[170] |
| | isoxsuprine | Affleck et al[171] |
| | naftidofuryl | Judge et al[172] |
| | papavarine | Brenconnier et al[173] |
| | pyrintol | Knezevic et al[174] |
| II. Anticoagulation | bishydrosycoumarin | Walsh et al[175] |
| III. Enhancing cerebral oxygenation | oxypentifyllin | Harwart et al[176] |
| | hyperbaric oxygen | Thompson et al[177] |

Table 5. Miscellaneous Agents Studied in Dementia

| *Agents* | *Selected References* |
|---|---|
| I. Psychostimulants | |
| methylphenidate | Darvill et al[178] |
| phthalazinol | Shimamoto et al[179] |
| II. Metabolic agents | |
| l-acetylcarnitine | Rai et al[180] |
| thiamine | Blass et al[181] |
| III. Other agents | |
| lithium | Brinkman et al[182] |

One possible explanation offered was that this group received a preventative effect of anti-inflammatory therapy. No direct evidence supports this claim so far.[158]

## X. CONCLUSION

The search for an effective cognition-enhancing therapy for AD has so far proved to be elusive, but has provided positive leads to develop further. The intense research activity generated by the proposition of the cholinergic hypothesis has failed to yield definitive results with the cholinergic drugs available. However, more potent and less toxic cholinesterase inhibitors are being developed and their preliminary positive effects in animals offer promise, as does the theoretical advantage offered by receptor-specific cholinergic agents. With increasing evidence of disruption of other neurotransmitter systems as well in AD, restitutive therapy aimed at multiple neurotransmitters may be more fruitful. As biomedical technology advances, prospects for alternative restitutive therapies appear increasingly feasible, including safer intracranial administration of drugs and implantation of modified neurons to either restore deficient neurotransmitter functions or express needed receptors.[3]

Significant progress in molecular biology in recent years has broadened the therapeutic options in AD beyond neurotransmitter-based strategies. Again, preliminary data from studies using neurotrophic and membrane-modifying agents appear promising. Localization of the gene for amyloid precursor protein on chromosome 21, where the familial Alzheimer's disease gene is also located, has been instrumental in bringing this ubiquitous, abnormal protein into the limelight. Attempts to understand amyloid pathogenesis may lead to means of preventing its accumulation, for instance with tachykinin peptides, if indeed intraneuronal and intrasynaptic deposition of amyloid is significant in the clinical expression of dementia in AD.

Future targets in the treatment of AD may also include excitotoxic brain aminoacids (e.g., glycine), or environmental toxins, as evidence of their role in the pathogenesis of this illness accumulates. Recent preliminary data offer hope that another avenue may be important to explore: namely, deficiencies in mitochondrial oxidation. Reduced function of cyrochrome oxidase, an enzyme in the electron transport chain complex, was reported in patients with AD,[183] and induced uncoupling of oxidative phospharylation resulted in cytoskeletal changes suggestive of those in AD.[184]

Drug trials in DAT have resulted in the direct positive results referred to, as well as several indirect positive benefits. Our knowledge of the neurochemical changes seen in the illness has greatly increased. This has led to a greater accuracy in the diagnosis of the disease and to better ways of investigating and evaluating the effects of cognition-enhancing drugs. Future drug studies would benefit by complementing these advances through the development of better animal models, the study of more, older, normal controls, since AD predominantly affects people over 65, and perhaps, the study of more patients with Down syndrome, almost all of whom develop AD pathology by the age of 40 years.

### *Acknowledgments*

These efforts were supported in part by grants from the National Institute of Mental Health (MH00733-05; MH40381-06).

The authors thank Maureen E. Herbstsommer for her secretarial assistance.

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